FINAL REPORT TO EUROPEAN OFFICE OF AEROSPACE RESEARCH AND DEVELOPMENT (EOARD)

BRIDGE-SUBSTITUTED [n]STAFFANES

SPC 98-4016

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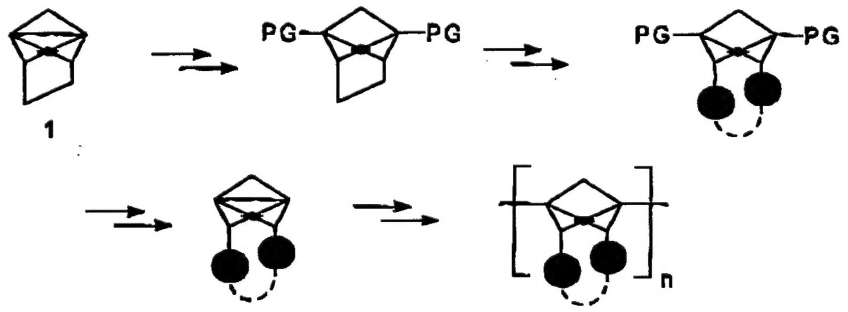
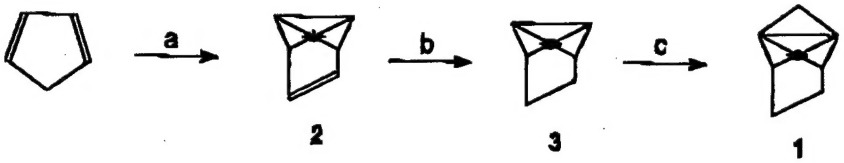
Bridge-substituted [n]staffanes has been proposed as new kind of laterally substituted rod-like molecules that could be a promising modules of a „molecular construction kit" and find their use for example in construction of 2D-molecular grids with active groups attached at arbitrary preselected positions directly to the rods of the construction. Many uses are planned for such "designer solids", from the production of regular arrays of extremely small quantum dots for flat panel displays or IR detectors, to the synthesis of barrier materials permeable to ordinary constituents of air or water but not to larger molecules.

Our way to synthesis of the bridge-substituted [n]staffanes planned to follow the Scheme 1. The synthesis starts from 2,4-ethano[1.1.1]propellane **1** that is transformed into bicyclo[1.1.1]pentane derivative with protected 1,3-bridgeheads. The ethano bridge in positions 2- and 4- has to be then converted into more useful functionalities that will play the role either of connectors either of active groups itself. Important is also the parallel configuration of such groups originating in the ethano bridge. Then, after deprotection of the bridgeheads, 2,4-substituted [1.1.1]propellane will be re-formed, that will yield target laterally substituted [n]staffanes by oligomerization reaction[1]. In addition, some bicyklo[1.1.1]pentane derivatives bearing suitable substituents on bridgeheads can be coupled[2] yielding staffanes as well.



Scheme 1

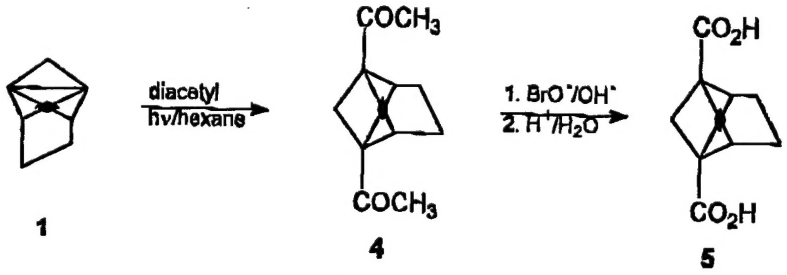
2,4-Ethano[1.1.1]propellane **1** was prepared according to Szeimies' procedure.[3] The synthesis starts from benzvalene[4] **2** that was prepared from cyclopentadiene, then reduced[5] to tricyclo[3.1.0.0^{2,6}]hexane **3**, that after dilithiation and reaction with chloroiodomethane gave propellane **1** in about 40 - 60 % yield (Scheme 2).



Scheme 2

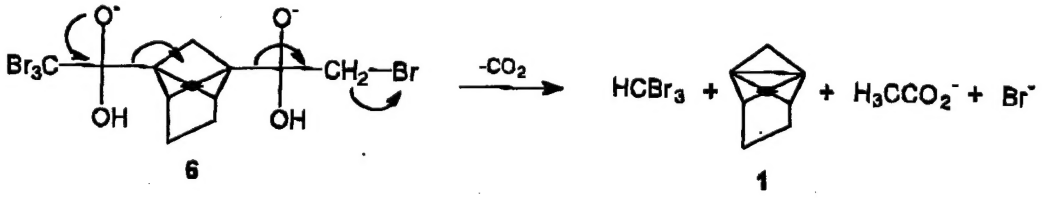
(a) 1. MeLi/Me_2O, -40 °C; 2. CH_2Cl_2; 3. BuLi. (b) N_2H_2. (c) 1. 2 eq. BuLi/ether; 2. CH_2ICl.

[1.1.1]Propellanes are well-known to add various radicals across C1-C3 bond giving 1,3-substituted bicyclo[1.1.1]pentanes or their oligomers - staffanes.[1] Photoaddition of diacetyl was successfully completed yielding 1,3-diacetyl-2,4-ethanobicyclo[1.1.1]pentane (**4**). The diketone **4** was oxidized to 1,3-dicarboxylic acid **5** in a haloform reaction, that was known to be successful in bicyclopentane and staffane series[6] (Scheme 3).



Scheme 3

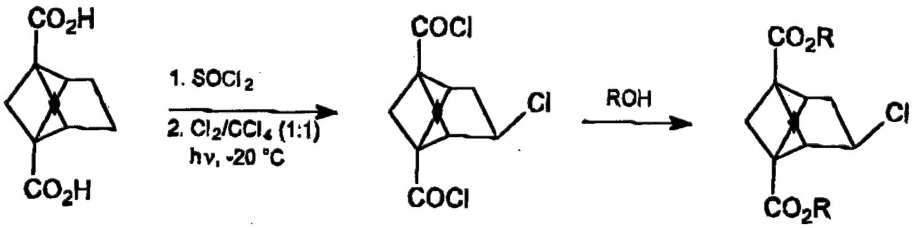
It was found that carrying out the reaction in an inverted manner, namely by the addition of hypobromite into the solution of diketone, led to substantial increase of reaction yield (from 50 % to 75 %), probably because of removing a possible interaction of partially brominated substituents at the both bridgehead positions (*cf.* Structure **6**) that could lead to fragmentation of molecule (Scheme 4). In the reaction conditions we used, the simultaneous bromination of both methyl groups of the same molecule was suppressed.



Scheme 4

A derivatization of bicyclo[1.1.1]pentane cage by substitution of hydrogens of methylene bridges is very difficult; therefore, only a few such reactions has been known yet. Besides of smooth fluorination[7], chlorination[8] as well as chlorocarbonylation[9] require strong conditions. In the light of these facts, we supposed that halogenation of our 2,4-ethanobicyclo[1.1.1]pentane derivatives will prefer the methylenes of 2,4-ethano bridge not requiring such strong conditions. We hoped that the halogenation-dehydrohalogenation reaction sequence would result in transformation of the ethano bridge into an unsaturated etheno one that would be relatively easy transformable into more 'interesting' functionalities.

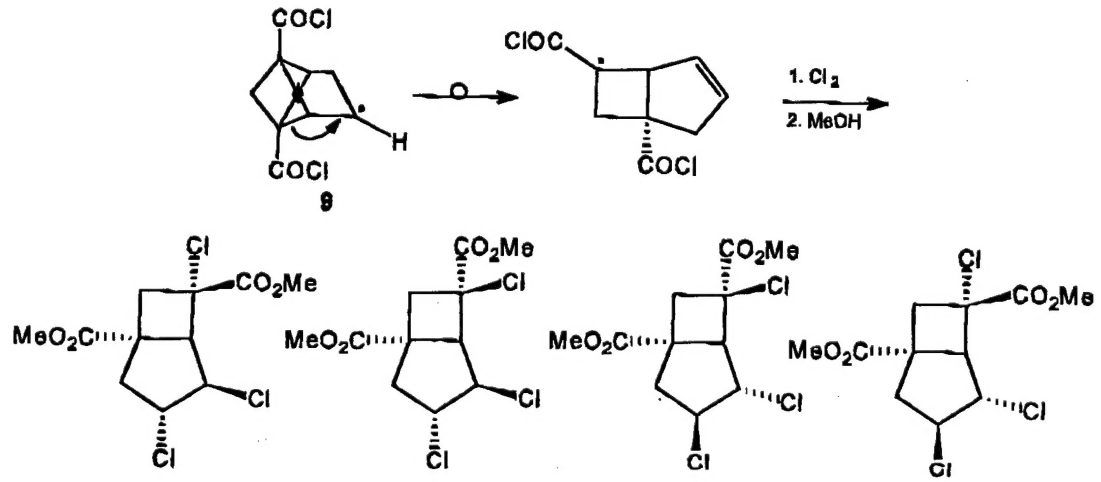
We have tried bromination of the bridge first. However, no brominated product was detected in the reaction mixture even after refluxing of dichloride of diacid **5** in almost neat bromine under irradiation or in the presence of dibenzoylperoxide. So, we turned to chlorination. After number of experiments, optimal conditions of the chlorination were found that are, again, not very mild. The diacid dichloride was reacted in a chlorine/carbon tetrachloride mixture (approx. 1:1) at -25 to -20 °C. In this conditions, presumably a monochloroderivative **7** was formed (Scheme 5) besides of acceptable amounts (about 10 %) of dichloroderivatives, and a complex mixture of higher chlorinated products. The monochlorinated product was isolated as various esters **8** (R = CH_3, $C(CH_3)_3$, $CH_2C_6H_5$).



5 **7** **8**

Scheme 5

Lowering the temperature of chlorination below -30 °C dramatically decreased the reaction rate with almost no effect on the ratio of products. On the other hand, higher reaction temperature resulted in formation of presumably trichloroderivatives, as detected by GC-MS. Since small or no formation of monochloro and dichloro derivatives were detected during the reaction at higher temperature, we assumed that the main four trichlorinated products detected are open cage compounds formed by rearrangement of an intermediate radical **9** and by subsequent fast chlorination of an olefinic intermediate (Scheme 6).



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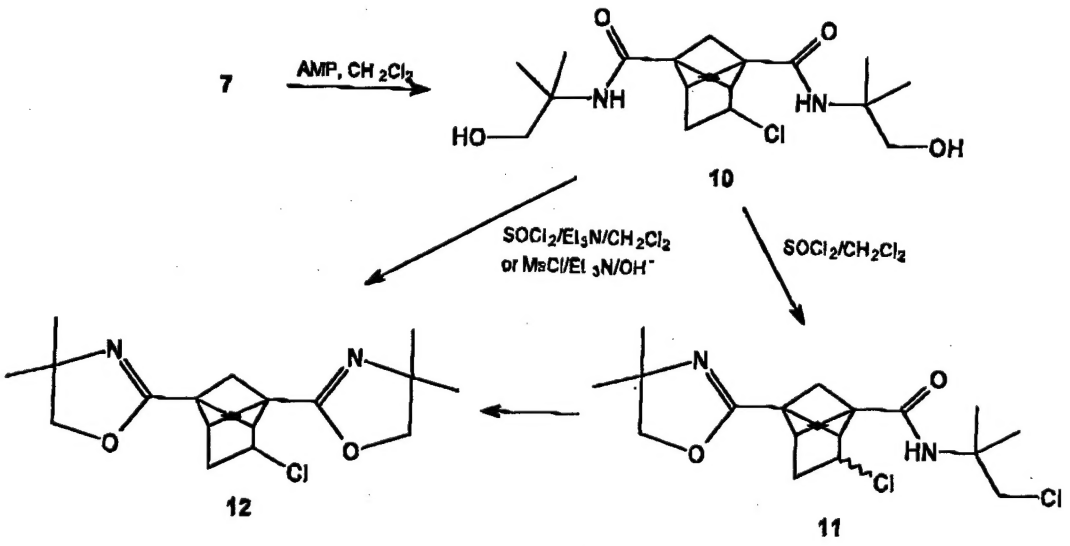
Scheme 6

Elimination reaction on rigid cyclic structures can be complicated by stereochemistry of substrates. Since the reaction requires *trans*- or *cis*-position of eliminated groups[10], it often fails due to steric effects in compounds where such configuration is impossible. In the case of our monochloroderivative, only *cis*-elimination can take place, which is little bit less preferred than

the *trans*-one. Moreover, the situation is also complicated by the fact that a very strained olefin is expected as a product.

Our attempts to eliminate HCl from esters **8** by means of corresponding alkoxides failed, unfortunately. Whereas, no changes were observed at low temperature (except transesterification when methyl ester was tried with *t*BuOK), a decomposition reaction took place during reflux in alcohol or THF. When lithium diisopropylamide (LDA) was used, formation of N,N-diisopropylamide was observed even at low temperature.

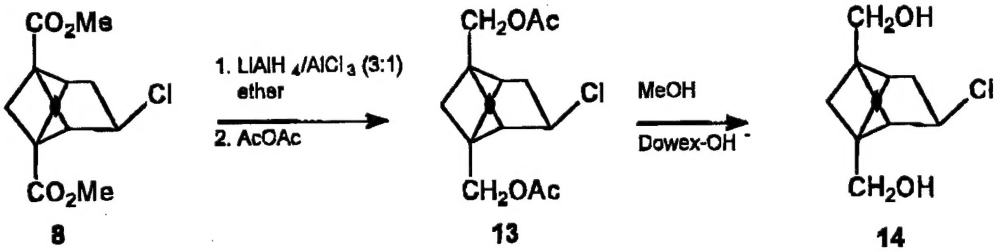
In order to have possibility of using stronger bases to eliminate HCl, we decided to protect the bridgehead carboxyls with more stable protective groups. Dimethyloxazolidine group was chosen that should protect carboxyl even against bases as strong as butyllithium[11]. Standard procedure[12] of its preparation starting from diamide **10** prepared from diacid dichloride **7** and 2-amino-2-methylpropanol (AMP) yielded only monooxazoline **11**, but slightly modified protocol, previously used by Denmark for preparation of chiral bisoxazolines[13], gave finally the bisoxazoline **12**, however, in low yield (Scheme 7).



Scheme 7

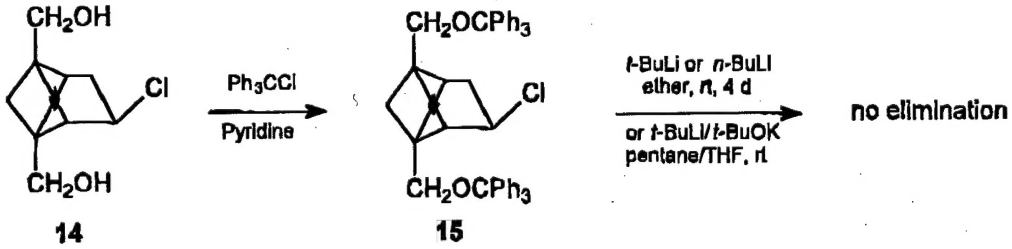
Optimization of preparation of the bisoxazoline **12** were stopped, when we realized that strong bases such as butyllithium and *tert.*-butyllithium did not react with it at low temperature. When the reaction temperature was increased, the bases attacked the isoxazoline groups yielding a complex mixture of non-cage products. Thus, oxazoline did not offer sufficient protection of bridgehead carboxyls. Since this group is one of the most stable protective groups used in protection of carboxyl[11], it seemed to be necessary to change also the group that had to be protected. We decided, therefore, to reduce the bridgehead carboxyls into hydroxymethyl groups that can be protected as various ethers with an outstanding stability in basic conditions. In addition, the primary hydroxylic groups can be easily transformed back to carboxylic ones by number of selective and mild oxidation methods[14].

The dimethyl ester **8** was reduced using alane in diethylether, by the method that should tolerate halogen in the structure[15]. Indeed, the reduction ran smoothly. In order to avoid difficulties often connected with isolation of product from aluminum salts after quenching the reduction with water, the product was separated as diacetate **13** after an acetic anhydride work-up[16]. Diol **14** was then prepared in moderate yield by an alkaline methanolysis using an anion-exchanger Dowex® as a catalyst (Scheme 8).



Scheme 8

From the variety of ether groups frequently used to protect hydroxyl, the triphenylmethyl ether was chosen for following reasons: (a) it is stable enough to survived even an alkyllithium attack; (b) deprotection needs relatively mild conditions which is important due to strained cage structure of bicyclo[1.1.1]pentane derivatives; (c) the same protective group can be used in proposed subsequent reaction of target olefin; (d) the introduction of bulky triphenylmethyl groups into the structure may improve crystallization and, therefore, purification of product. Indeed, a crystallinic bistrityl derivative **15** was prepared after the literature procedure[17] by the reaction of diol **14** with tritylchloride in pyridine (Scheme 9).



Scheme 9

However, the elimination of hydrogen chloride from **15** with n-butyllithium and/or tert-butyllithium did not work. The reaction with n-BuLi was carried out for four days at room temperature, but no elimination was observed. We did not observe even any indication of chlorine abstraction due to chlorine/lithium exchange. The derivative **15** remained unreacted even after reaction with superbase[18], a mixture of *tert.*-butyllithium and potassium *tert.*-butoxide.

Conclusions

A bicyclo[1.1.1]pentane derivatives have been prepared with protected bridgehead position (1,3) and an ethano bridge between positions 2- and 4-. The substituents in the bridgehead positions make possible a way back to propellane precursors of corresponding substituted staffanes. However, the proposed transformation of ethano bridge into some other, more attractive, functionalities is still under investigation. The only successful method of derivatization of this bridge has been found to be a chlorination, that was optimized to give a good yield of monochlorinated derivative with chlorine on the bridge. But the next step, the hydrogen chloride elimination, that would yield an olefin, suitable for proposed transformations, still failed. The number of bases were tried including as strong ones as butyllithium or its mixture with *tert.*-butoxide without any success.

Since we still account the laterally substituted staffanes for promising class of compounds,

we continue seeking the way of their preparation. In our best opinion, there are at least three ways to be investigated. First, a transformation of the ethano bridge of bicyclo[1.1.1]pentane derivatives that would follow other scheme than the elimination; most probably a substitution of chlorine in compounds such as **15** by some other group activating the neighboring methylene. A facile rearrangement of the strained molecule in a Sn1 reaction has to be, however, taken in account. Second, in the beginning of the reaction scheme, the double bond of benzvalene can be oxidized yielding a corresponding diol that after protection can be used in reactions basically following the original proposal. Third, some other starting compound can be chosen. For example, an [1.1.1]propellane with more flexible, consequently more reactive (?), 2,4-propano bridge might also offer the way to the target compounds.

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This report results from a contract tasking Masaryk University as follows: The contractor will investigate the synthesis of axial, axial-2, 4-disubstituted [1.1.1] propellanes and their bicuclo[1.1.1]pentane precursors for use as rods for fixing the location and orientation of active groups (for example cha magnetic, or non-linearly polarizable groups). These rods will be used to construct modular building blocks which in turn will be used in the synthesis of new materials with pre-designed properties ('Designer Solids').

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